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**Assessment of Treatment of Neonatal Sepsis at Dr.Gaffar Ibnauf
specialized children's hospital – Khartoum – Sudan.**

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Dedication

To the soul of my great father.....

To my lovely mother and sisters.....

To all who stand by me in my live.....

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Abstract:

Introduction: Neonatal sepsis is considered as the most common cause of death at Dr.Gaffar Ibnauf specialized children's hospital – Khartoum – Sudan. Mortality rate due to neonatal sepsis at the hospital was 24% of the total death in the hospital.

Objectives: The objective of this study was to assess the treatment of neonatal sepsis, to develop strategy for rational use of antibiotics to reduce the risk of antibiotics resistance, to evaluate the record keeping system and to evaluate the follow of the protocol of treatment of neonatal sepsis in the hospital.

Methodology: The study was a retrospective study conducted at Dr.Gaffar Ibnauf specialized children's hospital – Khartoum – Sudan in the period of 9/ 2010 – 10/ 2010, tow hundred and twenty nine patients medication records out of 562 records were checked for type of antimicrobial treatment used and if supportive treatment was used, investigations done, duration of treatments, if the protocol was followed and the outcomes of these treatments. The data was analyzed using SPSS.

Results: Mortality rate was found to be 21.35% from total number of patient admitted and diagnosed as neonatal septicemia, CBC done for all patients (100%), Blood culture and Urine culture were not done for any studied cases (0%), all cases received supportive treatment (100%), 65.93% received Cefotaxime + Ampicillin +Cloxacillin combination was the most common used treatment, other combination were used with

variable frequencies, hospital protocol was followed in (21.9%) of the cases , 74.67% of patient were cured while 25.33% were dead.

Conclusion: The mortality rate due to neonatal sepsis was very high, supportive treatment is curial and had been used for all patients, protocol follow-up was ignored for most of the cases and the selection of antimicrobial was irrational and not based on the type of the infection or the isolation of the causative organism, which will lead to emergence of resistance. The record keeping system was good enough to provide the required information.

ملخص الاطروحه:

مقدمة: يعتبر الإنتان الوليدي هو السبب الأكثر شيوعا للوفاة في مستشفى د/جعفر بن عوف التخصصي للأطفال - الخرطوم-السودان. معدل الوفيات بسبب الإنتان الوليدي في المستشفى كان 24 ٪ من مجموع الوفيات في المستشفى.

الأهداف : كان الهدف من هذه الدراسة تقييم معالجة الإنتان الوليدي ، ووضع استراتيجية لترشيد استخدام المضادات الحيوية للحد من مخاطر مقاومة المضادات الحيوية ، لتقييم نظام حفظ السجلات وتقييم اتباع بروتوكول علاج الأطفال حديثي الولادة المصابين بتعفن الدم في المستشفى.

الطريقة : أجريت الدراسة في المستشفى بأثر رجعي في الفترة من عام 2010 / 9 -- 10 / 2010 ، تمت مراجعته وبحث مئتان وتسعة وعشرون ملف من أصل خمسمائة اثنان وستون ملف و تم فحص السجلات لنوع المضادات الحيوية المستخدمة ، وإذا تم استخدام المعالجة الداعمة ، والفحوصات التي أجريت للتشخيص المرض واختيار العلاج المناسب، ومدة العلاج ، وهل تم اتباع البروتوكول ونتائج هذه العلاجات. وتم تحليل البيانات باستخدام التحليل الإحصائي للعلوم الاجتماعية.

النتائج: وجد أن معدل الوفيات هو 21,35 ٪ من مجمل الوفيات بسبب الإنتان الوليدي، التحليل الكلى للدم اجري بنسبه 100%، لم يتم تزريع الدم والبول لمعرفة الاحياء الدقيقة المسببه للمرض وتحسسها للمضاد الحيوى المعين 0%، تلقى جميع المرضى علاجات مساعده 100%، تلقى 65,93 ٪) ، سيفوتاكسيم + أمبيسيلين + كلوكساسيلين الذي هو الأكثر بين العلاج المستخدمة واستخدمت بعض المضادات الحيوية الاخرى بنسب متفاوتة ،تم اتباع البروتوكول بمعدل (21.9 ٪) ، وشفى 74.67 ٪ من المرضى بينما 25.33 ٪ توفى.

الخاتمة: معدل الوفيات بسبب الإنتان الوليدي عالي جدا ، العلاجات الداعمة من الاهميه بمكان وتم استخدامها لجميع المرضى ، لم يتبع البروتوكول المخصص لعلاج المرض كليا واستخدام المضادات المضادات الحيوية كان غير رشيد ولم يتم الاختيار على اساس نوع الكائن المسبب للمرض او نوع المرض(تصنيفه) مما سيؤدي إلى ظهور اجيال مقاومه للمضادات المتوفرة حاليا وكان نظام حفظ السجلات جيدا بما فيه الكفاية لتوفير المعلومات المطلوبة.

List of abbreviations:

(GBS) = Group B Streptococcus.

(E. coli) = Escherichia coli.

(GI tracts) = Gastrointestinal tracts.

(GU tracts) = Genitourinary tracts.

(CRP) = C - reactive protein.

(WBC) = White Blood Cell.

(LBW) = Low Birth Weight.

(PROM) = Preterm Rupture of Membrane.

(CSF) = Cerebro Spinal Fluid.

(SIRS) = systemic inflammatory response syndrome.

(S. aureus) = Staphylococcus aureus.

(MRSA) = methicillin-resistant S. aureus

(NICU) = Neonatal intensive care unit.

(CoNS) = Coagulase-Negative Staphylococci

(CBC) = Complete Blood Count.

(BC) = Blood Culture.

(UC) = Urine Culture.

(S test) = Sensitivity test.

(CAC) = Cefotaxime+Ampicillin+Cloxacillin.

(CACV) = Cefotaxime+Ampicillin+Cloxacillin+Vancomycin.

(BG) = Benzyl Penicillin+Gentamycin.

(EONSFL) = Early Onset Neonatal Sepsis First line.

(LONSFL) = Late Onset Neonatal Sepsis First line.

(LONSSL) = Late Onset Neonatal Sepsis Second line.

(LONSTL) = Late Onset Neonatal Sepsis Third line.

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Chapter 1: Introduction and Literature Review

1.1-Introduction:

1.1.1-Defintion:

Neonatal sepsis is a clinical syndrome that resembles invasive infection, usually due to bacterial infections in the neonatal period with multiple signs and symptoms, sepsis is commonest cause of neonatal morbidity and mortality, it is estimated that 20% of all neonate develop neonatal sepsis¹, which is responsible for 40-50% of neonatal death in developing countries².

1.1.2-Classification and Etiology:

Neonatal Sepsis can be classified into tow main groups according to the onset of symptoms³:

Early onset which is present within the early 2 days (48hours) of life and late onset usually present after 2 days (48hours) or more from birth date.

Early onset is occurring during passage of the fetus through the birth canal. The principal organisms that cause early-onset infection include predominantly group B streptococcus (GBS), Escherichia coli (E. coli)⁴. The major risk factor for this type of neonatal sepsis is the asymptomatic colonization of the maternal gastrointestinal or genitourinary tracts⁵. The maternal GI or GU tracts are colonized by GBS in up to 30% of pregnant women. Risk factors for higher colonization rates include African American descent and diabetes⁶. Additional risk factors for early-onset infection include prolonged rupture of membranes, prematurity, male gender, low birth weight, maternal infection, and poor prenatal care⁷.

Late-onset infection occur after delivery, due to the organism that may be acquired from environment such as hospital or at home ,infections from common hospital pathogens, including bacteria (coagulase negative staphylococcal species), viruses, and fungi (Candida species). Neonates on antibiotics for any length of time are at higher risk for the developing late-onset infection, and also infants with central intravenous catheter, Such as percutaneously-inserted central catheter, an umbilical arterial line, or an umbilical venous line. Neonates that are on ventilators for other reasons than sepsis may acquire an infection in the hospital (nosocomialinfections)⁸

Late-onset neonatal sepsis may occur in infants after leaving the hospital, so the causative organisms is similar as in early-onset sepsis, GBS, E. coli and other Gram-negative species⁹.

1.1.3-Risk Factors:

- Ruptured membrane for prolonged period of time (more than 24 hours).
- Prematurity associated with premature rupture of membrane.
- Preterm labour with no adequate explanation
- Fetal distress without adequate explanation (fetal heart rate abnormalities especially fetal tachycardia, passage of meconium).
- Evidences of infection or maternal infectionn.
- Amniotic fluid with foul smelling or malodorous baby
- Indwelling vascular catheter.

1.1.4-Signs of Sepsis in the Newborn

Signs are nonspecific and subtle and can not be used as only method for diagnosis of neonatal sepsis and to distinguish among causing organism, the common signs include:

- Hypothermia, Fever and/or instable temperature.
- Respiratory distress.
- Apnoea and bradycardia
- Cyanotic episodes and unexplained jaundice and hepatomegaly.
- Poor feeding, irritability, lethargy and seizures.
- Hypoglycemia, hyperglycemia and unstable blood sugar.
- Abdominal distension and bile-stained aspirates
- Skin rashes and umbilical flare.
- Poor peripheral perfusion.
- Pallor.

1.1.5-Investigations:

1.1.5.1-Full blood count:

Differential white cell count (Normal WBC 10-30,000 x 10⁹/L) and percentage left shift (immature neutrophils/total neutrophil count). If >20% this is moderately predictive of sepsis, low WCC especially with neutropenia is also suspicious of sepsis.

1.1.5.2-Blood cultures:

For the isolation of the causative organism and for sensitivity tests.

1.1.5.3-Urine routine and culture:

For the isolation of the causative organism and for sensitivity tests.

1.1.5.4-Chest radiograph:

To confirm the diagnosis in some cases.

1.1.5.5-C-Reactive Protein

1.1.5.6-Gastric aspirate and skin/wound swabs:

Generally done at birth only.

1.1.5.7-Lumbar Puncture-Cerebrospinal fluid:

Needed for all cases of late onset and some cases in early onset sepsis

1.1.6-Treatment of Neonatal sepsis:

Treatment of neonatal sepsis can be categorized into two main groups: Supportive treatments which include (providing thermo-neutral environment, respiratory support, volume expanders and blood transfusion if needed¹⁰).

And antimicrobial treatment which is used based on onset of the infection and the causative organism according to the sensitivity test, and the duration of treatment depends on the type of the infection. Standard text books recommend 14-day antibiotic therapy for culture-proven neonatal sepsis¹¹.

1.1.6.1-Supportive treatment:

The importance of supportive therapy split from the good understand of sepsis and the systemic inflammatory response syndrome (SIRS) with the subsequent effects of hypotension, diminished perfusion, thrombocytopenia and coagulation. Splanchnic hyperemia in premature infants, as seen in adults SIRS is due to sepsis¹⁰.

For managing all sick infants effectively, electrolyte balance and fluid with proper observation of inputs and outputs records is crucial, with regular monitoring of serum electrolytes and blood glucose dyselectrolytemia can be avoided and euuglycemia can be maintained. Fluid intake can be assessed by using the volume and specific gravity of the urine.

Blood pressure should be undertaken regularly and so all other vital signs to avoid hypotension and accompanied shock.

Infant's condition may require some vasopressors Intropes (eg. Dopamine and Dobutamine) can be used¹².

Some cases may require the transfusion of frozen plasma and platelets.

The use of these compounds must be monitored to avoid any subsequent complications such as fluid overload or any unpredictable outcomes.

Central catheter must be removed if there any suspicion of sepsis and can be reinserted 3-5 days after stabilization of therapy.

Good monitoring of fluid input and output will maintain good blood pressure and permit proper perfusion of renal and so the danger of renal failure will be diminished.

All infants especially very low birth weight and preterm require supportive ventilation to improve respiratory status.

Total parental nutrition is essential for most patients and it is better to be tailored according to the patient needs¹³.

1.1.6.2-Antimicrobial therapy:

Beside to the supportive therapy to restore the vital signs, antimicrobial is also required for treatment of neonatal sepsis. The selection of antimicrobial agent is depend on the type sepsis and causative organism. As an example in the early onset sepsis its better to use a combination of agents that treat group B streptococcus as well as Gram-negative species. Useful agents include ampicillin and gentamicin, or ampicillin plus cefotaxime. They used in combination to be a broad spectrum of the most common pathogens in early-onset sepsis, they penetrate CNS excellently. Ampicillin and gentamicin is the first line for treatment of early sepsis¹⁴. Gentamycin need close monitoring of renal function.

For late-onset sepsis, the selection of antimicrobial should be knowledge of the causative organism after culture and sensitivity tests. Ampicillin and Gentamycin can be used empirically as in early onset neonatal sepsis if the causative agents are sensitive to them.

In the presence of central line treatment should cover *S. aureus* and coagulase-negative staphylococci.

In case of methicillin-resistant *S. aureus* or MRSA in infants with line infections, the first lines antimicrobial will be vancomycin, plus an aminoglycoside such as gentamicin, for empiric coverage of Gram-negative bacilli until the result of culture is received.

In case of non controlled bacteremia and the sepsis is still progressed with adequate selection of broad spectrum antibiotics and presences of

fungemia the infected central line must be removed. Neonates admitted to neonatal intensive care unit (NICU) from community, antimicrobial used must cover meningitis treatment. Cephalosporin of third generation (i.e., cefotaxime or ceftriaxone) plus ampicillin should be included in the empiric therapy.

The clinical progress and microbial result must be reviewed at 48 hours, stop therapy if patient is well and culture is negative, continue if there are signs of sepsis and culture is positive and if anaerobic infections is suspected add metronidazole.

Some antibiotics were reserved for resistant organism and used after sensitivity test is performed (eg. Meropenem, Aztreonam and imipenem).

For G-ve use Aztreonam, Meropenem is active against most bacteria except methicillin resistant saph aureus (MRSA).

Imipenem reported to cause seizures and should be avoided in neonates.

Guidelines for treatment of neonatal sepsis (Protocol of Gaafar Ibnauf specialized children's hospital-Khartoum-Sudan for management of neonatal sepsis):

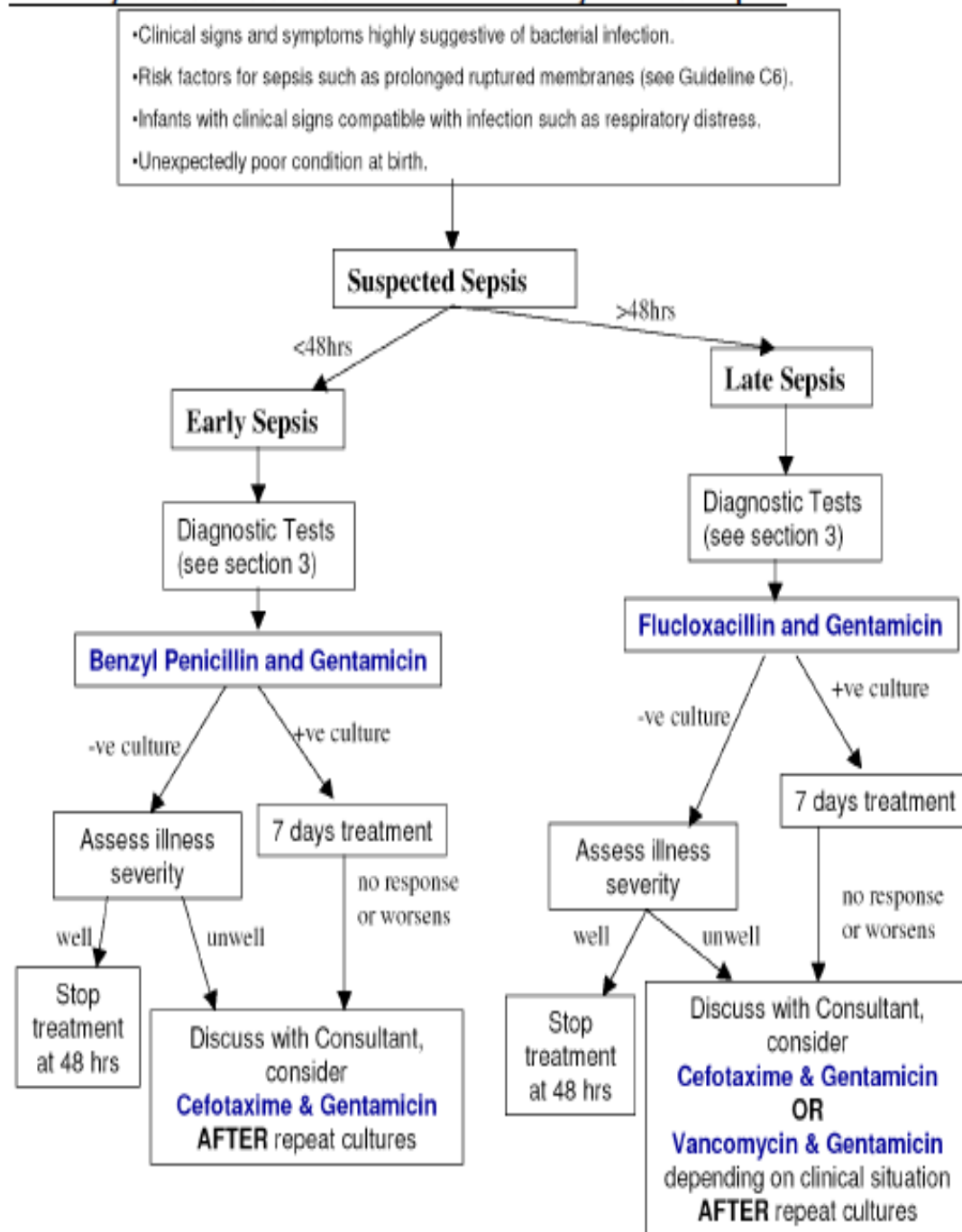
Early Onset Neonatal Sepsis	Late Onset Neonatal Sepsis
<p><u>First line:</u></p> <p>Ampicillin and Gentamycin</p>	<p><u>First line: Flucloxacillin and Amikacin</u></p> <p>Staphylococcus aureus is sensitive to Flucloxacillin.</p> <p>Coagulase negative staphylococcus is resistant to Gentamycin but sensitive to Amikacin.</p> <p>To cover Enterococci, strep faecalis, listeria and GBS Ampicillin must be added.</p> <p><u>Second line: Cefotaxime/Ceftazidime</u></p> <p>In case of meningitis and resistant klebsiella.</p> <p><u>Third line:</u></p> <p>If resistant staph or the patient is deteriorated or ill use Vancomycin and Amikacin.</p> <p>If pseudomonas is suspected use Piperacillin and Amikacin.</p>

Duration of treatment:

In general, empiric treatment of neonatal sepsis should be continued for 7-10 days, providing there is improvement in the overall condition of the patient. In many cases, the neonate will have all the clinical features of sepsis and will have improved after institution of antimicrobial therapy but will fail to yield a positive culture. In these instances it is appropriate to continue a full course (7-10 days) of antibiotics, despite the absence of a specific organism. Longer durations (up to 3 weeks) of antibiotic therapy may be used in cases of pneumonia or meningitis.

Type of infection	Duration of treatment/day
Positive septic screen and negative blood culture	7 – 10
Positive blood culture without meningitis	7 – 14
Urinary tract infection	7 – 10
Meningitis	21

Summary Sheet of Antibiotic Guidelines for Early and Late Sepsis



NB: If positive culture or clinical suspicion of specific site infection see guideline details (Pneumonia, Necrotising Enterocolitis, Meningitis, UTI, Endocarditis, Bone & Joint)

1.1.7-Rationale:

The number of patients admitted to Dr.Gaafar Ibnauf specialized children's hospital-Khartoum-Sudan and diagnosed as neonatal sepsis in the period of January 2010 up to October 2010 was 562, 120 patients were dead which represent 21.35% of the total number of the patients. Total number of patients dead in the this study period was about 500 death, the death due to neonatal sepsis in the hospital was 120 which represents 24% of the total death in the hospital.

This high percent of mortality due to neonatal sepsis reflect the fact that the sepsis was not managed efficiently.

The irrational use of antibiotics in the hospital will lead to emergency of resistance; moreover the cost of these medications is very high compared to the use of Benzyl Pecillin, Gentamycin and other effective –low cost agents which considered as a burden to the hospital budget.

Objectives:

General objective:

To assess the treatment of neonatal sepsis in Gaffar Ibnauf hospital.

Specific objective:

To develop strategy for rational use of antibiotics in the hospital.

To reduce the risk of antibiotics resistance.

To evaluate the record keeping system.

To evaluate the follow of the protocol of treatment of neonatal sepsis in the hospital.

1.2-Literature Review:

Auranqzwb B. and Hameed A. conducted study about the Neonatal sepsis in hospital –born babies: bacterial isolates and antibiotic susceptibility patterns, the objective of the study is to determine the frequency of bacterial isolates from neonatal blood cultures and their susceptibility patterns in hospital-born babies having sepsis. It was an observational study carried out at Obstetrics Unit and Special Care Baby Unit of Khyber Teaching Hospital, Peshawar from 1st January to 31st December 2001. This study was carried out on the neonates born and admitted in hospital with positive blood culture reports. Early onset neonatal sepsis and late onset neonatal sepsis were defined as illness appearing from birth to seven days and from eight to twenty-eight days postnatal age respectively. The blood culture reports were analyzed by SPSS package and cross tabulation was done. The result of the study was found to be: One hundred and twelve hospital-born babies presented with sepsis. Sixty-seven neonates had positive cultures. *Escherichia coli* (*E. coli*) was the commonest organism causing EONNS (35; 77.1%) followed by *Pseudomonas* (4; 8.9%), *Klebsiella* (4; 8.9%) and *Staphylococcus aureus* (2; 4.4%) respectively. In the late onset neonatal sepsis *E. coli* (19; 77.3%) was the commonest followed by *Staphylococcus* and *Pseudomonas* (2; 9% each) and *Klebsiella* (1; 4.5%). The gram-negative organisms showed high degree of resistance to commonly used antibiotics, ampicillin (79.3%), amoxicillin (74.6%) and ceftazidime (71.6%), cefotaxime (55.2%) and comparatively low resistance to gentamicin (43.2%), tobramycin (34.3%), imipinem (23.6%), amikacin (22.3%), ofloxacin and ciprofloxacin (11.9%) respectively. *Staphylococcus aureus* showed almost the same resistance to ampicillin,

75%, and comparatively low resistance to the rest of the antibiotics as compared to the gram-negative organisms.

The concluded that Neonatal sepsis is mainly caused by gram-negative organisms, which are developing resistance to commonly used antibiotics²¹.

B Muller-Pebody and his colleagues conduct study about the Empirical treatment of neonatal sepsis: are the current guidelines adequate? The Objectives of the study was to use national laboratory surveillance data to determine whether pathogens responsible for neonatal bacteraemia were sensitive to nationally recommended antibiotic regimens. Design All reports of neonatal bacteraemia received by the Health Protection Agency's voluntary surveillance scheme in England and Wales from January 2006 until March 2008, were extracted from the database. Organisms were ranked by frequency, and proportions susceptible to antimicrobials recommended for empirical treatment of neonatal sepsis were determined. Results There were 1516 reports of bacteraemia for neonates <48 h old (early-onset) and 3482 reports for neonates 2-28 days old (late-onset). For early-onset bacteraemia, group B streptococcus (GBS) was the most frequent pathogen (31%) followed by coagulase-negative staphylococci (CoNS; 22%), non-pyogenic streptococci (9%) and *Escherichia coli* (9%). For late-onset bacteraemia, CoNS were isolated most frequently (45%), followed by *Staphylococcus aureus* (13%), Enterobacteriaceae (9%), *E coli* (7%) and GBS (7%). More than 94% of organisms (early-onset) were susceptible to regimens involving combinations of penicillin with either gentamicin or amoxicillin, amoxicillin combined with cefotaxime or cefotaxime monotherapy. More than 95% of organisms (late-onset) were susceptible to gentamicin with either flucloxacillin or amoxicillin and amoxicillin with cefotaxime, but

only 79% were susceptible to cefotaxime monotherapy. Conclusions Current guidelines for empirical therapy in neonates with sepsis are appropriate. However, gentamicin-based regimens should be used in preference to cefotaxime-based treatments, because of lower levels of susceptibility to cefotaxime and the need to avoid exerting selective pressure for resistance. Surveillance data linked to clinical data should further inform rational antibiotic prescribing in neonatal units²².

T. B. Yves liem and his colleagues conducted a study which received 24 November 2009; returned 17 January 2010; revised 8 March 2010; accepted 8 March 2010 it was about variation in antibiotic use in neonatal intensive care units in Netherland, the Objectives of the study is to examine the variation in quantity and classes of antibiotics used in all 10 tertiary care neonatal intensive care units (NICUs) in the Netherlands during 2005. They collect data from all tertiary care NICUs in the Netherlands on clinical and demographic characteristics and the type and quantity of systemic antibiotic use [expressed as defined daily doses (DDD)/100 admissions] in 2005. Antibiotics were ranked by volume of DDDs, and those antibiotics which accounted for 90% of the total volume of use [drug utilization (DU) 90%] were noted.

They found that Antibiotic consumption ranged from 130 to 360 DDD/100 admissions. In total, 9–24 different antibiotics were used, of which 3–10 were in the DU90% segment.

They conclude that by comparing antibiotic use in Dutch NICUs they found a considerable variation in the number of different antibiotics used and in the total amount of antibiotic use. Further exploration of the opportunities to reach consensus in antibiotic policy, and to increase attention to antibiotic stewardship, is recommended²³.

Chapter 2:

Methodology:-

2.1-Study design:-

A retrospective cross-sectional study design was carried out in this research, the relevant data was collected from patient's files which contain the patients medication records using data collecting sheet which include the followings:-

- Patient file number.
- Patient sex.
- Patient age.
- Investigations done: - (Complete Blood Count, Blood Culture, Urine Culture and sensitivity tests).
- Antimicrobial treatment selected (Benzyl Penicillin, Gentamycin, Amikacin, Cefotaxime, Ceftriaxone, Metronidazole, Vancomycin, (ampicillin+Cloxacillin), Meropenem, Antifungal and Antiviral).
- Duration of treatments.
- Supportive treatment was used or not. (Yes or No).
- Protocol was followed or not. (Yes or No).
- Patient cured or not.

2.2-Study area:-

The study was carried at Dr.Gaafar Ibnauf specialized children's hospital-Khartoum-Sudan.

2.3-Study population:-

Patients admitted to Dr.Gaafar Ibnauf specialized children's hospital and diagnosed and treated for neonatal sepsis in the period from January 2010 up to October 2010.

2.4-Sample size:-

The sample size of this study was calculated using the following equation:-

$$n = \frac{N z^2 P q}{(n-1)d^2 + z^2 P q}$$

$$n = \frac{562 \times (1.96)^2 \times 0.5 \times 0.5}{561 \times (0.05)^2 + (1.96)^2 \times 0.5 \times 0.5} = \underline{229}$$

Where:

N = Population under Study.

n = Sample size.

Z = Value of normal curve corresponding to level of confidence (95% =1.96).

P = Proportion of target group.

q = 1-p.

d = desired margin of error 5%.

From the above mentioned equation the sample size of this study was equal to 229.

2.5-Criteria of selection:-

All patients diagnosed and treated for neonatal in the period from January 2010 up to October 2010 in all units at Dr.Gaafar Ibnauf specialized children's hospital-Khartoum-Sudan.

2.6-Method:-

Patients medication records were checked for the following:-

- Patient file number.
- Patient sex.
- Patient age.
- Investigations done: - (Complete Blood Count, Blood Culture, Urine Culture and sensitivity tests).
- Antimicrobial treatment selected (Benzyl Penicillin, Gentamycin, Amikacin, Cefotaxime, Ceftriaxone, Metronidazole, Vancomycin, (ampicillin+Cloxacillin), Meropenem, Antifungal and Antiviral).
- Duration of treatments.
- Supportive treatment was used or not. (Yes or No).
- Protocol was followed or not. (Yes or No).
- Patient cured or not.

2.7-Data analysis:-

The data was analyzed using Microsoft Excel Sheet and SPSS.

Chapter 3:

Result and Discussion:-

3.1-Results:-

During the period of the study 229 files and patients medications records were revised and checked for the followings:

Gender, Age, Investigations, Supportive treatment, Antimicrobial treatment, Duration of treatment, Protocol follow-up and Outcomes.

The following results were obtained after analysis of data.

Sex	Frequency	%
Male	123	53.71
Female	106	46.29
Total	229	100

Table No. (1) Gender

Age	Frequency	%
0-48 hours	20	8.73
More than 48 hours	209	91.27
Total	229	100

Table No. (2) Age

Early neonatal sepsis if age was 0 - 48 hours.

Late neonatal sepsis if age was more than 48 hours.

CBC	Frequency	%
Done	229	100
Not done	0	0
Total	229	100

Table No. (3) CBC.

Blood culture	Frequency	%
Done	0	0
Not dpone	229	100
Total	229	100

Table No. (4) Blood Culture.

Urine culture	Frequency	%
Done	0	0
Not done	229	100
Total	229	100

Table No. (5) Urine Culture.

Sensitivity test	Frequency	%
Done	0	0
Not done	229	100
Total	229	100

Table No. (6) Sensitivity Test.

Supportive treatment	Frequency	%
Provided	229	100
Not provided	0	0
Total	229	100

Table No. (7) Supportive treatment.

Medications used	Frequency	%
Bezyl penicillin inj+Gentamycin inj	15	6.60
Cefotaxime inj+Apmiclox inj(Cloxacillin+Ampicillin)	151	65.93
Cefotaxime inj+Apmiclox inj (Cloxacillin+Ampicillin) +Vancomycin inj	30	13.10
Cefotaxime inj+Apmiclox inj(Cloxacillin+Ampicillin) +Acyclovir inj+Fluconazole inj	1	0.20
Cefotaxime inj+Apmiclox inj(Cloxacillin+Ampicillin)+Meropenem inj	8	3.50
Cefotaxime inj+Apmiclox inj(Cloxacillin+Ampicillin) +Metronidazole inj	17	7.50
Cefotaxime inj+Apmiclox inj(Cloxacillin+Ampicillin) +Amikacin	5	2.20
Ceftriaxone inj+ Apmiclox inj(Cloxacillin+Ampicillin)	2	0.90
Total	229	100

Table No. (8) Antimicrobials used.

Duration of treatment	Frequency	%
0-2 Days	40	17.46
3-7 Days	150	65.50
Mores than 7 days	39	17.04

Table No. (9) Duration of treatment

Outcomes	Frequency	%
Cured	171	74.67
Death	58	25.33
Total	229	100

Table No. (10) Outcomes.

Follow up of protocol	Frequency	%
followed	50	21.9
Not followed	179	78.1
Total	229	100

Table No. (11) Follow up of treatment protocol.

3.2-Discussion:

During the study period and after calculation of the sample, 229 files and medication records of patients diagnosed and treated for neonatal sepsis were checked for Gender, Age, Investigations, Supportive treatment, Antimicrobial treatment, Duration of treatment, Protocol follow-up and Outcomes.

An epidemiological survey of neonatal sepsis in a hospital in western Nigeria carried out by DO Awoniyi and his colleagues they found that the prevalence of bacterial infection was higher in samples obtained from male (65%) neonates than from females (35%). The majority of the patients studied were aged between 1-9 days but the result did not differ significantly from other age group²⁴.

We found that the prevalence of neonatal sepsis in male was 53.71% Table (1) which is higher than in female 46.29 % (Table1), and that confirm the fact that male gender is considered as a risk factor for neonatal sepsis.

A study titled (Neonatal infections in England: the NeonIN surveillance network) Conducted by Vergnano S. and his colleagues Designed as prospective multicentre surveillance using a web-based database linked to 12 English neonatal units. They measure: Incidence, age at infection, pathogens and antibiotic resistance profiles. They found that the incidence of early onset sepsis (EOS; ≤ 48 h of age) was 0.9/1000 live births and the incidence of late onset sepsis (LOS; >48 h of age) was 3/1000²⁵.

In our study, the incidence of early neonatal sepsis to late neonatal sepsis were 8.73 % and 91.27 % respectively (Table 2), this high incidence of late neonatal sepsis indicate that the neonates acquired the causative microorganism from the surrounding environment either from hospital or home and that may be due to improper handling of the neonate or the low hygiene at home.

Complete Blood Count (CBC) is one of the diagnostic methods of infectious diseases.

In our study the CBC was performed for all cases 100% (Table 3).

The diagnosis of neonatal sepsis, the isolation of causative organism, and the proper selection of the most effective and efficient antimicrobial depend mainly on blood culture and urine culture.

In study conducted From February 2003 to December 2004, at Neonatal Unit of Ghurki Trust Teaching Hospital, attached with Lahore Medical & Dental College Lahore by Rizwan Waseem and his colleagues,

The objectives were to find out the bacterial pathogens in neonatal sepsis and to determine antimicrobial sensitivity patterns of these pathogens.

They found that *Escherichia coli* was the commonest organism isolated, followed by *Klebsiella*, *Pseudomonas*, *Staph. aureus*, *Staph epidermidis*, *Enterobacter*, *Acinobacter*, *Serratia* and *Streptococcus*. *E. Coli* constituted 33.37% of the early onset group, and 33.33 of late onset group.

Klebsiella constituted 34.37% and 22.22% while *Pseudomonas* 12.5% and 13.88% of early and late onset groups respectively. *Enterobacter* spp. was present only in the late, while *Streptococcus* in the early onset sepsis. *Acinobacter*, *Staph. aureus* and *Staph. Epidermidis* affected both the early and late onset groups²⁶.

In our study 0% of the studied cases had been blood cultured (Table4), and 0% urine cultured (Table5), no isolation of the causative organisms and the selection of the antimicrobial treatment was done empirically, this led to irrational use of antibiotics which will lead to emergence of resistance to these agents used.

The selection of the best antimicrobial treatment based on the sensitivity of the isolated organism to the specific antimicrobial agent.

The study above mentioned²⁶ was also aimed to determine the sensitivity of the isolated pathogens to different antimicrobial agents.

They found that all of the isolated were having a low sensitivity to Ampicillin, Gentamicin and Cefotaxime, while most of the organisms were sensitive to Ceftazidime, Amikacin and Imipenem. E. coli showed sensitivity of 14.70% to Ampicillin, 17.6% to Gentamicin, 41.17% to Cefotaxime, 61.76% to Amikacin, 79.4% to Ceftazidime and 97.05% to Imipenem.

Klebsiella and Pseudomonas also showed a low sensitivity to Ampicillin, Gentamicin, and Cefotaxime, while good sensitivity to Amikacin, Ceftazidime and Imipenem²⁶.

In our study no blood culture 0%(Table 4), and/or urine culture 0%(Table 5) were performed, so neither isolation of causative microorganisms nor sensitivity test 0%(Table 6) were done. Antimicrobial agents were chosen regarding less to causative organisms and this also shows an irrational use of antibiotics in the hospital and of course the emergence of resistance to the used agents.

We found that supportive treatments (Intravenous fluids, Human albumin, Parental Nutrition, Thermal and Incubation) were received by

all of the sample patients 100% (Table 7) as recommended in management of neonatal sepsis for maintenance of neonate vital signs.

A study about the Empirical treatment of neonatal sepsis: are the current guidelines adequate? Was conducted by Muller-Pebody B and his colleagues the objectives of the study were to use national laboratory surveillance data to determine whether pathogens responsible for neonatal bacteraemia were sensitive to nationally recommended antibiotic regimens.

All reports of neonatal bacteraemia received by the Health Protection Agency's voluntary surveillance scheme in England and Wales from January 2006 until March 2008, were extracted from the database.

Organisms were ranked by frequency, and proportions susceptible to antimicrobials recommended for empirical treatment of neonatal sepsis were determined.

They found that More than 94% of organisms (early-onset) were susceptible to regimens involving combinations of Penicillin with either Gentamicin, Amoxicillin combined with Cefotaxime or Cefotaxime monotherapy. More than 95% of organisms (late-onset) were susceptible to Gentamicin with either Flucloxacillin or Amoxicillin and Amoxicillin with Cefotaxime, but only 79% were susceptible to Cefotaxime monotherapy.

And concluded that Current guidelines for empirical therapy in neonates with sepsis are appropriate. However, Gentamicin-based regimens should be used in preference to Cefotaxime-based treatments, because of lower levels of susceptibility to Cefotaxime and the need to avoid exerting selective pressure for resistance ²⁷.

In our study the antimicrobials agent used were as following:

The most of the patients 65.93% were received the combination of Cefotaxime and Ampicillin plus Cloxacillin (Ampiclox) (Table 8), and it was prescribed regardless to blood culture, urine culture and sensitivity tests, this regimen which contain Ampicillin and Cloxacillin was used for the concern about Ampicillin which was recommended by the most of protocols in combination with either Gentamycin injection, Amikacin injection or third generation cephalosporin (eg.Cefotaxime), but the presence of Cloxacillin make it one of the drawbacks of this regimen because it will lead to development of resistant organisms, the Gentamycin-based regimen (in combination with Benzyl Penicillin inj) was prescribed for only 6.6% of the patients(Table8), and as mentioned in the above study conclusion²⁷, the Gentamicin-based regimens should be used in preference to Cefotaxime-based treatments, because of lower levels of susceptibility to Cefotaxime and to avoid development of resistant microorganisms²⁷.

The second most used combination was Cefotaxime inj+Apmiclox inj (Cloxacillin+Ampicillin) +Vancomycin inj represents 13.10% (Table 8) which also prescribed regardless to blood culture, urine culture and sensitivity tests, the addition of Vancomycin injection to this regiment due to susceptibility of MRSA infection, Vancomycin was added after the delay in recovery of patients. The use of this combination must be restricted for resistant cases and after isolation of causative organism and sensitivity test which was totally ignored in all of these cases, and the consequences of this irrational use of antibiotics are the generation of resistant microorganism and the high economical burden on hospital budget.

The third most used combination was Cefotaxime inj+Apmiclox inj(Cloxacillin+Ampicillin) +Metronidazole inj 7.5% (Table8),

The Metronidazole was added to cover aerobic and anaerobic microorganism but also regardless the causative agent.

Combination of Gentamycin injection and Benzyl Penicillin injection prescribed for only 6.6% of patients (Table8), this regimen which Gentamycin-based was recommended by lot of authorities²⁸, but it was rarely used and this maybe due to the fear of treating doctors from resistant organisms and the severe illness of the neonates admitted to the hospital .

Cefotaxime inj+Apmiclox inj(Cloxacillin+Ampicillin)+Meropenem inj combination prescribed for 3.5% of the patients(Table 8), this combination was also used regardless the isolation of the causative organisms and Meropenem inj was added due to the delay in response to the Cefotaxime inj+Apmiclox inj(Cloxacillin+Ampicillin) combination and the severe illness of the neonate , in spite of the fact that it's reserved drug and not recommended for use in pediatric patients, and can be used for patients hospitalized for long periods and patients with complicated conditions who tried other antibiotics without improvement.

Cefotaxime inj+Apmiclox inj(Cloxacillin+Ampicillin) +Amikacin combination used for 2.2% of the patients (Table 8), to cover most of organism, it was used regardless the isolation of causative organism and this also may lead to emergence of resistance.

Ceftriaxone inj+ Apmiclox inj(Cloxacillin+Ampicillin) combination used for 0.9% of the patients (Table 8), it wasn't recommended as first line but

due to lack of knowledge of causative organism it was used as empiric therapy and this also may lead to emergence of resistance.

Cefotaxime inj+Apmiclox inj(Cloxacillin+Ampicillin) +Acyclovir inj+Fluconazole inj combination used for 0.2% of the patients (Table 8) to cover all suspected infections bacterial, fungal and viral (Neonatal sepsis can be of bacterial and/or fungal and/or viral infections)⁸, this is considered as empiric therapy to cover all possible infections .

There are different protocols regarding the use of antimicrobial in managing neonatal sepsis, here we will stick to the protocol approved and used in the hospital which is the study area.

There are different lines for treatment of neonatal sepsis based on the type of infection and the causative organism as stated in the introduction, the follow-up of these lines were studied, and the results were:

Early onset neonatal sepsis first line (Ampicillin or Benzyl Penicillin injection and Gentamycin) used for 6.6% of the patients.

Late onset neonatal sepsis first line (Flucloxacillin and Amikacin) was not used for any case 0% (table 8).

Late onset neonatal sepsis second line (to the first line adds Cefotaxime/Ceftazidime) was not used for any case 0% (table 8).

Late onset neonatal sepsis third line (Vancomycin 13.10% and Amikacin 2.2%) (Table 8).

The hospital protocol was followed in 21.9% of the studied cases.

The duration of treatment as mentioned in the introduction vary from 48 hours up-to more than three weeks.

Gathwala G, and his colleagues conducted a study titled: Ten days vs. 14 days antibiotic therapy in culture-proven neonatal sepsis. The objective of the study was to compare the effectiveness of a 10-day course of antibiotic therapy with the conventional 14-day course in blood culture-proven neonatal sepsis. They concluded that Ten-day antibiotic therapy is as effective as 14-day therapy in blood culture-proven neonatal sepsis, if the infant has achieved clinical remission by Day 7 of therapy²⁸.

In our study the duration of treatment for the studied cases were: 17.46% of patients were treated for 0 – 48 hours , 65.50% of patients were treated for 3 – 7 days which represent the most common duration of treatment and 17.04% of studied cases treated for more than 7 days due to very severe sepsis (Table 9).

Outcomes of the treatment for the studied cases were found to be as following:

The improved and cured and discharged neonates were 74.67% of the studied cases Table (10).

The percent of the patient not cured was 25.33% Table (10) which is high percent that indicates the need for establishing strategies to reduce this high mortality rate.

Chapter 4:

Conclusion and Recommendations:-

4.1-Conclusion:

Mortality rate due to neonatal sepsis at Dr.Gaffar Ibnauf specialized children's hospital – Khartoum – Sudan was 24% of the total death in the hospital, 562 patients were diagnosed and treated as neonatal sepsis, 120 patients out of the 562 patients were dead which represents 21.35% of the neonatal sepsis patients, the diagnosis was done depending mainly on clinical signs and CBC, all patients received supportive treatment , the selection of antimicrobial was empirically not based on blood or urine culture or sensitivity tests, the most used combination was Cefotaxime+Ampicillin+Cloxacillin which represent 65.93% (Table 8) for all types of neonatal sepsis regardless the causative organism, some cases treated using other combination when the above mentioned treatment failed to treat the case effectively and efficiently, which include Cefotaxime+Ampicillin+Cloxacillin+Vancomycin combination used in 13.1% (Table 8), in which vancomycin was added after the suspicion of MRSA without cultures, Cefotaxime inj+Apmiclox inj(Cloxacillin+Ampicillin) +Metronidazole inj combination used for 7.5% (Table8) to cover anaerobic infections, Cefotaxime inj+Apmiclox inj(Cloxacillin+Ampicillin) +Acyclovir inj+Fluconazole inj used in 0.2% (Table 8) for very ill neonate to cover as possible infections. Cefotaxime inj+Apmiclox inj(Cloxacillin+Ampicillin)+Meropenem inj combination

prescribed for 3.5% (Table 8). Cefotaxime inj+Apmiclox inj (Cloxacillin+Ampicillin) +Amikacin combination used for 2.2% of the sample cases (Table8). Ceftriaxone inj+ Apmiclox inj (Cloxacillin+Ampicillin) combination used for only 0.9% of the patients (Table 8). Finally Benzyl penicillin inj+Gentamycin inj combination which used for 6.6% of the patients (Table 8).

The protocol of the treatment of neonatal sepsis was followed only in 21.9% of the studied cases and that indicate to an irrational use of antibiotics in most of the studied cases,

The outcomes of the treatment was 74.67% of the patients were cured and 25.33% of the patients were not cured (died) either due to improper selection of antimicrobial or the severity of the illness in which the patients arrived the hospital in a complicated conditions and very severe sepsis.

The records keeping system in the hospital was proper, but more effort is needed to use computer database to make it easier to evaluate different treatment for different diseases and to easy the access to patient's medication records without violence of privacy and confidentiality of patients.

4.2-Recommendations:

New strategies should be established in order to reduce this high mortality rate and the irrational use of antibiotics.

The selection of antimicrobial for treatment of neonatal sepsis must be based on the type of the infection and the isolation of causative organism through blood culture, urine culture and sensitivity tests.

Pharmacist as health care provider and because they are familiar with medication must be more involved in prevention of irrational use of antibiotics, so antimicrobial stewardship team is to be created which include at least infectious disease physician, clinical pharmacist with infectious diseases training and clinical microbiologist to optimize the selection of appropriate antimicrobial agents, dose and duration and that will lead to best outcomes and reduce emergency of resistance due to irrational use of antimicrobial agents.

Soft copies of patient's medication records must be kept to make it easier to assess each treatment individually and to easy the access by treating staff with out violation of privacy and confidentiality of the patients.

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